

**Advisory Committee on Blood Safety and Availability**  
**April 7-8, 2004**  
**Meeting Minutes**

The meeting was called to order by Jerry A. Holmberg, PhD, Executive Secretary of the Advisory Committee on Blood Safety and Availability. The conflict of interest statement was read by Ms. Olga Nelson. The meeting was then turned over to the Committee Chairman, Dr. Mark Brecher who recused himself from chairing the meeting due to research interest in the subject matter and to avoid any perception of conflict. Since Dr. Brecher is a subject matter expert in the main topic of the meeting, he remained available throughout the meeting to provide factual information to the committee. The Executive Secretary appointed Mark Skinner, JD Chairman pro tem. The following were provided as updates to the Committee:

- 1) Dr. Holmberg reported that the recommendations from the last meeting regarding the role of the Federal Government in maintaining the nation's blood supply are currently under review by Dr. Beato, Acting Assistant Secretary for Health. The concept of a National Blood Reserve has been favorably received and a progress report will be forthcoming at the next Committee meeting.
- 2) Captain Lawrence McMurtry shared with the Committee the plans to enhance the current DHHS Sentinel Site blood supply monitoring system by incorporating it into the Secretary's Command Center. It will have some attributes of the FDA's TransNet prototype for open reporting but will rely on sentinel hospital and blood center sites.
  - a) Blood centers will be added to the Blood Availability and Safety Inventory System (BASIS) in 2004 and more hospital transfusion service sites in 2005.
  - b) Quantitative data elements are expected to include total units and group O (pos. and neg) red cells and apheresis and whole blood-derived platelets. There will be information about inventories, collections, utilization and outdating.
  - c) Qualitative elements about shortages will continue to be collected, as well as daily reports.
  - d) The data are expected to support broad, long-term assessments of the status and direction of the nation's blood supply and improve the knowledge base underlying Departmental policy decisions.
  - e) It will also help with critical incident response planning. It is not

intended to support regular government involvement in day-to-day operations and decisions of transfusion services or blood centers in the local communities.

- 3) The implementation of the Medicare Modernization Act (MMA) was discussed by CMS Representatives, Ms. Cynthia Read and Dr. James Bowman III. The MMA was enacted on December 8, 2003. Dr. Bowman provided a summary of the MMA which was posted on the Advisory Committee's web site.
  - a) Basically the Medicare payment system depends on where the services are rendered and by whom.
    - i) Approximately 90 per cent of blood is provided in the inpatient hospital setting in an acute care hospital. This is controlled by the DRG system, established in 1983. Under the MMA, there will be additional monies but not necessarily to support blood and blood products.
    - ii) The hospital outpatient department is another setting and by and large, a good portion of the blood that is used in this setting is reimbursed under the Hospital Outpatient Prospective Payment System (HOPPS).
      - (1) Prior to MMA, Medicare basically paid for drugs in the outpatient hospital setting under different methods.
        - (a) Ambulatory Payment Categories (APC)
        - (b) High cost items at the time of implementation of HOPPS were given "transitional pass-through status" or transitional pass-through payment.
      - (2) Ms Read explained that the ruling for 2003 for determining whether or not an item would be packaged was \$150 has been lowered to \$50. The MMA states that the \$50 should be the threshold for 2005 and 2006. Also changes to Section 1842 (o) under the MMA for physician office setting for establishing payments for pass-through drugs will also pertain to how pass-through drugs will be paid under the HOPPS.
      - (3) The ruling for HOPPS was published on January 6, 2004.

When it was published, it was recognized that some items may have been missed and the public had the opportunity to comment. Those items misclassified have been corrected in the April release. System modifications are implemented quarterly. Transmittal 113 or change request 3145 describes payment rate changes for 28 drugs, biologicals, and radio-pharmaceuticals, some of which resulted from the reclassification of those items from multiple-source to single-source drugs.

- (4) Section 303 (e) of the MMA provides a mechanism for the Secretary to make some adjustments in blood clotting factor payments. Plasma protein derivatives will be modified since they are considered under the law as “drugs.” Some (e.g., IVIG) are statutorily exempt from new competitive bid requirements, but others (e.g., clotting factors) are not.
  - (5) Ms Read announced that rule making for 2005 will probably be published in July. There will be a sixty-day comment period. For 2004, CMS accepted its Advisory Committee’s recommendation and froze the payment rate for blood and blood products at the 2003 level.
  - (6) In February 2004, the APC Panel recommended again the use of external data for its evaluating the cost of blood and blood products and CMS should make adjustments accordingly.
- iii) Finally, there is the physician office setting which is provided for under a completely separate authorization, i.e., Physician Fee Schedule. Payment for blood is essentially unchanged and will remain for physicians at 95% of the average wholesale price. Clotting factors will fall under Section 1842 (o) of the MMA. The Secretary may substitute other percentages based on data and information provided by the manufacturers to CMS prior to January 1, 2004. Competitive bidding for certain drugs and biologicals will become effective January 1, 2006, however, the Secretary has exclusion authority.
- b) MMA conference agreement says that the Secretary is directed to compile and clarify the procedures and policies for billing for blood and blood cost

in the hospital inpatient and outpatient settings, as well as the operation of the collection of the blood deductible.

- 4) Ms. Elizabeth Callahan, FDA, discussed the final rule on Bar Code Label Requirements for Human Drug Products. The new regulations, to enhance patient safety will be effective April 26; will require drugs including plasma protein derivatives to be identified within two years by bar codes (UCD, linear, National Drug Code with lot numbers and expiration dates optional) making them match to patients and physicians' orders. Biologics (CBER) will require a machine readable (which will permit new technologies other than bar codes acceptable) with the same time limit. Lot number and outdate label requirements are unchanged.

**Main Meeting Topic: The impact and the assessment of methods to reduce the risk of bacterial contamination of platelet products.**

- 1) Dr. Holmberg refreshed the memory of the committee on recommendation made at the January 2003 meeting regarding three of the major issues addressing the blood community, i.e., bacterial contamination of platelet products, clerical errors, and Transfusion Related Acute Lung Injury (TRALI). Dr. Beato asked the Committee to look at the impact of 100% quality control and assessment of methods to reduce the risk of bacterial contamination in platelet products. Dr. Holmberg asked the Committee to consider eight questions in their deliberations:
  - a) Has there been an impact on the availability of apheresis and whole blood-derived platelets for patient use?
  - b) Has there been a shift in type of platelet products available?
  - c) If so, has there been a shift in economics as a result of the implementation of methods to reduce the risk of bacterial contamination and platelet products?
  - d) Has detection of bacterial contamination of whole blood-derived platelets been limited to hospitals?
  - e) Has the endpoint method to detect bacterial contamination of whole blood platelets been sufficient for sensitivity and specificity?
  - f) Does the federal government need to establish policies for methods for reduction of bacterial contamination and platelet products?
  - g) Are data sufficient to establish such a policy?

- h) Is there additional research that needs to be conducted in the area of methods for reduction of bacterial contamination and platelet products?
- 2) Dr. Kathleen Sazama, President of the American Association of Blood Banks, presented both a historical review of the issue as well as the AABB current Standard for Accreditation.
- a) In 2002, the FDA approved two devices for quality control of bacterial contamination.
  - b) The AABB promulgated a Standard (5.1.5.1), effective March 1, 2004, that blood banks or transfusion services shall have methods to limit and detect bacterial contamination in all platelet components
- 3) Dr. James AuBuchon, on behalf of the College of the American Pathologists (CAP) presented data to support the CAP Phase I Requirement.
- a) A similar requirement (Phase I) was implemented, December 2, 2002, by the CAP for their accredited laboratories.
  - b) More than four million units of platelets are transfused each year, which leads to more than 100 cases of death due to bacterial contamination.
  - c) Hospital transfusion services would rather that blood centers take the responsibility for qualifying a whole blood-derived platelet unit for transfusion, and blood centers feel that they do not have the right tools to address the problem with whole blood-derived platelets. As a result, although apheresis units are generally being cultured today by the blood center that collect them, whole blood derived platelets units are not being cultured, but are being examined by techniques that are much less sensitive and more likely to give false positive results.
  - d) Culturing is usually performed on the day after collection in order for the bacterial inoculum to multiply to the point that it can be detected in a small sample. Based on the work of Drs. AuBuchon and Brecher, a culture that is truly positive, with the most commonly encountered contaminants, can usually be detected in 12 to 20 hours of culture. Therefore most blood centers hold units for 24 hours after culturing before sending them to the hospitals in order to prevent them having to recall a unit from the hospital or even worse, having to deal with the transfusion of a positive cultured unit.

- e) Dr. AuBuchon pointed out that the FDA wants ironclad statistical proof before extension of platelets to seven days is permitted, and that implies performing a trial on more than 50,000 units at a cost of more than \$2 million. He went on to explain that manufacturers of culture systems have nothing to gain by such as study and are unwilling to pay for a trial.
- 4) Dr. Jaro Vostal presented the FDA's current thinking on several broad areas that include sample diversion pouches in whole blood collection kits, detection of bacteria in platelet products, and also alternate platelet storage up to seven days.
- a) Dr. Vostal pointed out that contamination at the collection is very low, and there needs to be time to allow bacterial proliferation in the product to reach detectable levels. This is usually 24 to 48 hours.
  - b) Sampling too early can lead to a sampling error. If a larger sample of volume is taken, it improves the sensitivity but depletes the product. All these variables have to be balanced against one another.
  - c) Clearance of bacterial detection devices used for QC of platelet products relied on in vitro (spiking) studies.
  - d) The bacterial risk of future products should not be greater than the risk of a five-day platelet screen for bacterial contamination with a FDA-approved method or device.
- 5) Mr. A.C. Marchionne of BioMerieux presented the Committee with an overview of their culture system.
- a) The system consists of both an aerobic and anaerobic culture vial, however, many blood centers are currently only using the aerobic system.
  - b) The system is based on a sensor that detects Carbon Dioxide and comparison with three different algorithms.
- 6) Dr. Jerry Ortolano of Pall presented the Enhanced Bacterial Detection System (eBDS).
- a) Pall's eBDS system measures oxygen in the head space and compares it to some predetermined threshold limit.
  - b) Bacterial concentrations less than 5 CFU per ml are often complicated by inconsistent growth.

- 7) Preliminary data from several large blood centers presented to the HHS Advisory Committee on Blood Safety and Availability for apheresis platelets (tested with the BioMerieux BacTAlert) in April 2004 are summarized in the table below:

|                          | True Positive | False Positive | Number Tested |
|--------------------------|---------------|----------------|---------------|
| New York Blood Center    | 5 (1/4,101)   | 5 (1/4,101)    | 20,506        |
| Florida Blood Services   | 6 (1/1,790)   | 5 (1 /2,147)   | 10,737        |
| Puget Sound Blood Center | 5 (1/1,800)   | 15 (1/600)     | 8,999         |
| Total                    | 16 (1 /2,515) | 25 (1/1,1610)  | 40,242        |

- 8) Multiple presentations attested to little change in the availability of platelets with CAP Phase I Requirement implementation. Most of those affected by this standard appear to be using rapid techniques (swirling, acceptable by the CAP but not recommended by the AABB; or pH/glucose, which are acceptable to either). The March 1, 2004 implementation of the AABB Standard seemed to have little net additional effect. Nevertheless, there were signs of stress in the system.
- a) Many, but not all, reported a reduction in the production and use of whole blood derived platelets.
  - b) Most reported logistical problems with losing 36-48 hours (for one major center, this was ½ day more subtracted from shelf-life available before culturing) were added to up front in the 5-day storage of apheresis platelets, but mostly patients got what they needed.
  - c) Outdating has increased, but has seemed to have been manageable. This appears to be midweek.
  - d) One transfusion service reported a clinical demand for fresh platelets; most of the 250-400 whole blood-derived and 10-45 apheresis-derived platelets transfused each day are used within 30 hours of collection. Although dipstick analysis (pH/glucose) whole blood derived pools and culture apheresis units are performed on the products, none have sufficient time for any bacteria present to multiply and be detected.

- 9) Several manufacturers briefed the Committee on currently approved technologies which might reduce bacterial contamination of platelets. These include using elemental iodine (vs. organic iodine) and alcohol or chlorhexidine to prepare the venipuncture site and diverting the first 30-40 ml of collected blood to a side pouch to be used for testing.
- a) The “new” prep has been widely implemented without difficulty.
  - b) Although the precollection diversion pouch has been widely used in Europe and in Canada, two of the three suppliers to the US market have had problems with test sample hemolysis or dilution by anticoagulant. Steps are under way to correct these difficulties.
- 10) Dr. Dirk de Kort of the Sanquin Blood Foundation presented the Dutch experience with reduction of bacterial contamination of platelet products.
- a) In Europe and in much of the rest of the world, whole blood derived platelets are harvested from the buffy coat after a hard spin; they must be diluted for use, encouraging the development of additive solutions that could increase storage time.
  - b) Pre storage pooling is encouraged.
  - c) Bacterial culture is mandatory in many European countries, some for more than a year.
  - d) An apheresis-derived platelet product is approved for seven day storage, provided a licensed procedure for reducing the risk of bacterial contamination is used.
- 11) Discussion throughout the two days and comments from many presenters encouraged the acceptance in the US of pre storage pooling of whole blood-derived platelets and of extended dating of all platelets to seven days.
- a) It was not clear if the plastic in the bags tentatively approved for seven day apheresis platelet storage in the US was the same as that in bags used to harvest whole blood-derived platelets.
  - b) Further, it is not clear if buffy coat derived platelets are similar enough to platelet-rich plasma derived platelets that pre storage pooling and prolonged shelf-life would not be different.

- c) “Points to Consider” for accepting any bacteria test as a product release criterion includes:
  - i) Contamination of blood at collection is very low, necessitating time for bacteria to proliferate to detectable levels;
  - ii) Too early sampling can lead to sampling error;
  - iii) Larger samples improve detectability but deplete the product;
  - iv) Current detection devices require 24-48 hours for growth to be detectable; and,
  - v) Detection is based on metabolically active bacteria and may not detect endotoxin.
- d) Determining sensitivity, specificity and predictive value of early product cultures are currently believed to require large and expensive field trials (sample size 30,000 - 50,000).
- e) Storage containers in use in the US have not been validated for pre storage pooling of whole blood-derived platelets harvested with a platelet-rich plasma technique (see below), nor for extending storage beyond five days from collection.

The committee unanimously passed four Recommendations to be addressed to the Secretary.

1. Whereas a safe, available and affordable blood supply is an essential National resource; and whereas the committee applauds Secretary Thompson recognition of the importance of sound policy or reimbursement, the DHHS ACBSA:
  - 1) reiterates the recommendations of their January 28 & 29, 2004, meeting relevant to blood and blood products, including plasma-derived therapeutics and their recombinant analogs,
  - 2) endorses the MMA Conference report statement, “The Secretary is directed to compile and clarify the procedures and policies for billing for blood and blood cost in the hospital inpatient and outpatient setting as well as the operation of the collection of the blood deductibles.”,

- 3) urges timely action in response to the above directive and the aforementioned recommendations of the committee.

Vote: 9 affirmative, 0 nays, 0 abstentions (1 member left the room)

2. Whereas blood clotting factors are life saving biologic therapies; and whereas it is crucial that individuals with hemophilia have access to and choice of the full range of blood clotting factors available on the market; and whereas inappropriate reimbursement methodologies can have a significant and detrimental impact on Medicare beneficiary access to these therapies; and whereas a competitive bidding process under Medicare Part B (Sec 1842 (o)(1) c) of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) would not assure access to blood clotting factor, and whereas Congress has recognized the unique challenges facing beneficiaries who rely upon life sustaining plasma protein therapies through an exclusion of intravenous immune globulins (IVIG) therapies from competitive acquisition provisions of the MMA, the Committee recommends that the Secretary exclude blood clotting factors from competitive acquisition under the Exclusion Authority granted in Sec. 1847B(a)(1)(D).

Vote: 10 affirmative, 0 nays, 0 abstentions

3. Whereas a competitive acquisition section of the MMA (section 302) contains language that may require an establishment of quality standards and accreditation bodies for blood products and transfusion medicine services; and whereas adequate federal regulatory controls and public and private standard setting and accreditation bodies exist and are effective, the committee requests that the Secretary should use his authority contained in the MMA to exclude all blood products and transfusion medicine services from the establishment of quality standards and competitive acquisition provisions of the MMA.

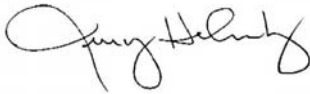
Vote: 10 affirmative, 0 nays, 0 abstentions

4. Whereas the DHHS ACBSA recognizes the importance of methods to reduce the risk of bacterial contamination in both apheresis and whole blood derived platelets; and whereas the committee also recognizes the potential for limited availability of platelets, particularly whole blood derived platelets and whereas the current five-day shelf life of apheresis and whole blood derived platelets and restrictions on whole derived platelets pre storage pooling has been identified as barriers to the optimal implementation of bacterial detection in platelets, the committee encourages dialog among the DHHS agencies, blood programs, and manufacturers to ensure strategies for:

- Facilitation of prompt development of technologies;
- The design and completion of feasible studies; and
- The satisfaction of licensing requirements to permit both the pre storage pooling of whole blood derived platelets and extension of platelet dating.

Vote: 7 affirmative, 0 nay, 2 abstention (1 member left the room)

Submitted by:



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Certified by:



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